Published in final edited form as:

J Neurosci Methods. 2014 January 15; 221: 196–201. doi:10.1016/j.jneumeth.2013.10.009.

Setting a gold standard for quantification of leukoaraiosis burden in patients with ischemic stroke: the Atherosclerosis Risk In Communities Study

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Abstract

Background—Accurate and reliable measurement of leukoaraiosis, or MR-detected white matter hyperintensity (WMH) burden in subjects with acute ischemic stroke (AIS) is important for ongoing research studies and future models of risk and outcome prediction, but the presence of a cerebral infarct may complicate measurement. We sought to assess accuracy of a volumetric method designed to measure WMH in AIS subjects as compared to the previously validated protocol.

New Method—We randomly selected and equally sampled 120 brain scans from the Atherosclerosis Risk in Communities (ARIC) MRI Study individuals within designated mild, moderate, and severe tertiles of WMH volume (WMHV). T2 FLAIR axial images were analyzed using the AIS WMH volumetric protocol and compared with the ARIC (gold standard) method. Pearson correlation coefficients, linear concordance correlation coefficient, and Blant-Altman procedures were used to assess measurement agreements between the two procedures.

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Author Disclosure:

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. This work was also supported by NIH R01-HL70825 (T.M.), NINDS K23NS064052 (N.S.R.), the American Heart Association/Bugher Foundation Centers for Stroke Prevention Research, and the MGH Deane Institute for Integrative Study of Atrial Fibrillation and Stroke.

Dr. Natalia Rost is supported by the National Institute of Neurological Disorders and Stroke (K23NS064052).

Dr. Salomeh Sadaghiani reports no disclosures.

Dr. Alessandro Biffi is supported by the American Heart Association Bugher Foundation.

Ms. Kaitlin Fitzpatrick reports no disclosures.

Ms. Lisa Cloonan reports no disclosures.

Dr. Jonathan Rosand reports no disclosures.

Dr. Dean Shibata reports no disclosures.

Dr. Thomas Mosley is supported by the National Institute of Health (R01-HL70825).

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Results—Median WMHV determined by using the ARIC method was 7.8cm^3 (IQR 5.7–13.55) vs. 3.54cm^3 (IQR 2.1–7.2) using the AIS WMH method. There was good correlation between the two measurements ($r=0.52, 0.67$, and 0.9 for tertiles 1, 2, and 3 respectively)($p<0.001$).

Comparison with Existing Method—the AIS WMH protocol was specific for leukoaraiosis in ischemic stroke, but it appeared to underestimate WMHV compared to the gold standard method.

Conclusions—Estimates of MR-detectable WMH burden using a volumetric protocol designed for analysis of clinical scans correlate strongly with gold standard measurements. These findings will facilitate future studies of WMH in normal aging and in patients with stroke and other cerebrovascular disease.

Search Terms

all cerebrovascular disease/stroke; volumetric MRI; white matter hyperintensity; leukoaraiosis; small vessel stroke

1.1 Introduction

Severity of leukoaraiosis identified as T2 white matter hyperintensity (WMH) on brain MRI in aging adults is an established marker of stroke and chronic functional sequelae of cerebrovascular disease, including cognitive and psychomotor impairment (de Groot et al, 2000; Henon et al, 2003; Kuller et al, 2004; Prins et al, 2004b; Smith et al, 2004; Vermeer et al, 2003). Identifying the burden of WMH and measuring its progression is critically dependent on the methodology, which throughout the years evolved from using semi-quantitative approaches to highly automated, volumetric methods (Black et al, 2009; DeCarli et al, 1992; Fazekas et al, 2002; van Straaten et al, 2006). Prior data indicate that the visual WMH rating scales compare favorably to each other and to volumetric measurement of leukoaraiosis when measured in healthy aging adults (Kapeller et al, 2003; van den Heuvel et al, 2006; Prins et al, 2004a). However, no data exist to assess the performance of volumetric algorithm devised to quantify severity of WMH in subjects with manifest cerebrovascular disease such as acute ischemic stroke (AIS).

Study of WMH in AIS subjects represents a unique challenge given the clinical nature of brain MRI scans limited by the lack of protocol standardization and possible artifacts, especially due to motion (Mantyla et al. 1997; Skare et al, 2007; Wang et al, 2005). T2 FLAIR hyperintensities reflecting acute ischemic injury and non-WMH artifacts in these subjects must be strictly excluded from the analysis of leukoaraiosis burden in AIS subjects in order to assure validity of WMH measurement (Rost et al 2010a). In prior reports, a semi-automated, volumetric method of WMH burden assessment in subjects with acute, manifest cerebrovascular disease (including ICH and AIS) demonstrated a high degree of inter and intra rater reliability (Gurol et al, 2006; Irizarry et al, 2005; Rost et al, 2010b). However, no data exist to assess the accuracy of this protocol as compared to the existing gold standard methods of WMH analysis (Mosley et al, 2005).

In this study, we sought to determine whether a previously validated, semiautomated volumetric method designed to assess WMH severity in patients with stroke is accurate in comparison to the accepted gold standard method used for WMH burden assessment in the Atherosclerosis Risk in Communities (ARIC) study.

1.2.1 Methods

1.2.2 Population

Design details and sampling strategy of the ARIC study, a prospective, population-based study of 15,792 US individuals, have been previously published (ARIC, 1989). The current analysis is based on the original ARIC cohort participants who contributed to the ARIC MRI Study (2004–2006) (Gottesman et al, 2010). The individuals who had an initial MR scan at the third ARIC examination (n=1,812) were recruited for a follow up brain MR scan and cognitive testing (Knopman et al, 2011). At the third ARIC examination, all individuals aged >55 years and living in Forsyth County (NC) and Jackson (MS) were invited for brain MRI, with exception of participants excluded due to prior surgery for an aneurysm in the brain; metal fragments in the eyes, brain, or spinal cord; valvular prosthesis, cardiac pacemaker, cochlear implant, spinal cord stimulator, or other internal electrical device; and occupations associated with exposure to metal fragments (2% of women and 6% of men). MRI scans of sufficient quality were available for 1,812 subjects (Knopman, et al, 2011). The individuals in whom silent brain infarcts were discovered on MRI despite no reported history of transient ischemic attack or stroke were excluded from further analysis.

For this project, the imaging data included 120 randomly selected and equally sampled MRI scans from individuals enrolled in the ARIC MRI Study with WMH grades designated as mild, moderate, or severe based on the WMH volume (WMHV) distribution tertiles within the total ARIC MRI subset.

1.2.3 Neuroimaging analysis

We analyzed in random order 120 axial FLAIR images of 3 mm section thickness using a semi automated, volumetric method for measurement of WMHV in AIS subjects (the AIS WMH method). Neuroimaging analysts (S.S., K.M.F., N.S.R.) were blinded to the WMH grade or WMHV tertile assigned to each scan based on severity of leukoaraiosis.

1.2.4 WMH volumetric analysis: the AIS WMH method

The method for WMHV assessment in subjects with stroke has been previously described in detail (Irizarry, et al, 2005; Rost, et al, 2010a, 2010b). All scans were converted from DICOM to Analyze format using *MRICro* software (University of Nottingham School of Psychology, Nottingham, UK, www.mricro.com) for computer-assisted determination of WMHV. All sequential hemispheric T2 FLAIR sections were included in the analysis. First, the supratentorial WMH region-of-interest (ROI) maps were derived using the overlap between automated signal intensity thresholding, which was followed by manual editing, as necessary (Figure 1). We have excluded the cerebral structures that are prone to T2-hyperintensity artifact, such as basal ganglia and thalamus (calcifications), as well as the mesial temporal areas, cortico-medullary junction line, and ventricular (ependymal) lining from this analysis. Hyperintense signal from prior cerebral infarcts were not considered WMH and the corresponding brain regions were masked, as were those with motion artifact. To avoid confounding by hyperintensity signal resulting from acute cerebral ischemia in the original AIS WMH protocol, the total WMHV was derived by doubling the WMHV obtained from the hemisphere contralateral to AIS (Rost 2010a). Because the ARIC scans were obtained in stroke-free individuals, the final WMHV in this study was obtained as a sum of WMHV from the both hemispheres. Finally, the total intracranial volume (TIV) measured on T1 sagittal MRI was used to normalize WMHV for head size (Ferguson et al, 2005). High inter rater reliability for WMHV measurements using this method with ICC of 0.92 and 0.98 were previously reported (Chen et al, 2006).

1.2.5 WMH volumetric analysis: the ARIC method

The total WMHV was estimated as the sum of periventricular and subcortical white matter signal abnormality on axial FLAIR images segmented into voxels assigned to 1 of 3 categories based on signal intensity (normal brain, cerebrospinal fluid, or leukoaraiosis) (Jack et al, 2001). The automatically generated leukoaraiosis maps using *FLAIR histoseg* (Jack et al, 2001) were manually edited to exclude infarcts and other non WMH lesions. The ARIC study delivered a mean absolute error of 6.6% and a test retest coefficient of variation 1.4% for leukoaraiosis volume. TIV was manually measured from T1 weighted sagittal MR images, and the total WMHV volume was standardized to a mean TIV of 1500 cm³.

The same images were graded using a semi quantitative 10-point scale by visual comparison with eight standards which successively increased from barely detectable white matter changes (Grade 1) to extensive, confluent changes (Grade 8). Furthermore, studies with no white matter changes received Grade 0, and those with changes worse than Grade 8 received Grade 9 (Liao et al, 1997).

1.2.6. Comparison of the two WMH volumetric analysis methods

The similarities and differences between the two WMH volumetric analysis methods are presented in Table 1.

1.2.6 Statistical analysis

All statistical analyses were performed using STATA 10.0. Continuous numerical variables are expressed as mean $\pm$ standard deviation (SD) with the exception of WMHV, which is expressed as the median $\pm$ inter-quartile range (IQR). Original WMHV measurements (in cm³) were natural log transformed for analysis. Pearson correlation coefficients and linear concordance correlation coefficients were calculated. Linear concordance correlation coefficient, Bland Altman, and Bradley Blackwood analyses were carried out to assess accuracy, precision, and reliability of the two measurements used in this study (Altman and Blant, 1983; Barnhart et al, 2002; Bradley and Blackwood, 1989). Significance threshold was set at two sided p value <0.05.

1.3. Results

The ARIC MRI Study cohort included 1,949 individuals aged 55–72 years (mean 62.5 years, SD 4.5), of whom 51% of individuals were of African-American and 49% of Caucasian origin (Gottesman et al, 2010; Knopman et al, 2011). Silent brain infarcts were found in 11% of all individuals despite no reported history of transient ischemic attack or stroke. MRI scans of these participants were excluded from the total cohort considered in this analysis.

Based on the volumetric measurements of WMH obtained from 120 brain MRI scans, total median WMHV was 3.54 cm³ (IQR 2.11–7.19) vs. 7.88 cm³ (IQR 5.7–13.55) using the AIS WMH and the ARIC methods, respectively (Figure 2). Variation between the total WMHV was apparent within each tertile of leukoaraiosis based on the segmentation approach (Table 2); however, correlation between the WMHV measurements was good, ranging from moderate ($r=0.52$ and 0.67 , for the first and second tertiles, respectively) to high ($r=0.9$ for the third tertile), all $p<0.001$. Although linear concordance correlation coefficient for all WMHV measurements was 0.80 (SD 0.025) ($p<0.001$) with Bland Altman analysis indicating acceptable correlation between the two methods (mean difference in WMHV $=5.79$ cm³ (95% difference 4.84 – 6.7 cm³; limits of agreement $= -4.47$ to 16.6 cm³), the degree of discrepancy in WMHV measurements using the two methods appeared to be correlated to severity of WMH (Figure 3).

Of 120 ARIC subjects with WMHV measured using volumetric method, 106 (88.3%) had been graded by the original ARIC investigators on the ARIC visual rating scale (grade 0 to 9). Of these, 2 subjects (1.9%) had WMH grade 0, 36 (33.9%) had grade 1, 37 (34.9%) had grade 2, 14 (13.2%) had grade 3, 7 (6.6%) had grade 4, 6 (5.6%) had grade 5, 3 (2.83%) had grade 6, and 1 (0.9%) had grade 7 of WMH burden. Despite significant difference in median WMHV corresponding to the combined WMH grade categories, tertiles of WMHV normalized to the TIV as described in the methods using the two volumetric protocols correlated closely to the median WMH grade (Spearman $\rho = 0.85$ for the ARIC visual grade and WMHV derived using the AIS WMH protocol and Spearman $\rho = 0.82$ for the ARIC visual grade and WMHV derived using the ARIC WMH protocol, both $p < 0.001$) (Table 3).

1.4 Discussion

Severity of leukoaraiosis in patients with acute stroke is strongly linked to clinical and cerebral tissue outcomes; therefore, accurate quantitative assessment of WMH may be essential in prediction of stroke recovery and recurrence (Arsava et al, 2009; Ay et al, 2008). However, no data currently exist to demonstrate the accuracy of WMH quantification in subjects with AIS. We report the results of a direct comparison study between the volumetric measurements of WMH obtained using an existing rigorously validated technique for leukoaraiosis assessment, and the volumetric method designed to assess severity of leukoaraiosis on clinical MRI scans of subjects with acute cerebral ischemia (Mosley et al, 2005; Rost et al, 2010a). We determined that the two volumetric techniques were strongly correlated; however, there was a significant discrepancy between them based on the distribution of WMHV values within the cohorts. Considering that the two protocols were designed to measure the same characteristic (WMHV) under the variable study conditions (e.g., different study population, research setting, goals of study etc), correlation estimates may carry limited information regarding the accuracy and precision of the data collected using these protocols. Using concordance correlation coefficient instead provides additional information on precision (degree of variation) and accuracy (degree of scale shift) of the agreement between the two measurements; however, as a measure of reproducibility, concordance correlation coefficient does not quantify the degree of agreement between the two protocols (Altman and Blant, 1983; Barnhart et al, 2002; Bradley and Blackwood, 1989).

Our data indicate that the AIS WMH method tended to underestimate measurements for WMHV, as compared to the ARIC method. This trend is not fully unexpected and, in part, it may be a requisite outcome of this direct method comparison considering that the AIS WMH volumetric protocol was designed to assess WMHV in subjects undergoing evaluation for acute stroke. In these subjects, the heterogeneity of clinical MRI scan acquisition parameters and possibility of artifact from acute ischemic changes and/or excessive motion may invalidate WMH quantification, unless specificity of the method is assured. The AIS WMH WMHV protocol was designed purposely to maximize the specificity of leukoaraiosis assessment in subjects with AIS; furthermore, this is emphasized in the training procedures for AIS WMH protocol (Rost et al, 2010a, 2010b; Skare et al, 2007). On the contrary, the ARIC technique have been optimized to some degree to detect early stages of mild WMH in a healthy cohort largely without artifacts associated with an inpatient population; and thus, a more inclusive thresholding was set for the automated segmentation (Figure 4). We are encouraged that our volumetric technique performs conservatively in comparison to this protocol rigorously tested for accuracy and reproducibility (Jack et al, 2001) in the past, and yet it's strongly correlated with the ARIC WMHV values.

Another explanation for discrepancy in absolute values of WMHV acquired using these two methods is that greater variations in the overall volume of WMH may result from relatively small variations in the intensity thresholds between the methods, given that most WMH lesions have a low surface area-to-volume ratio. However, these absolute discrepancies translate into at least moderate-to-high estimates of correlation between the two techniques. Furthermore, based on the further exploration of the measurement agreement between the two methods, an appreciable association between the mean values and the difference between the estimates (Blant Altman analysis) is likely related to the measurement error range using both techniques. (van den Heuvel et al, 2006; van Straaten et al, 2006).

Volumetric estimates of leukoaraiosis in our study correlated closely with the WMH grades previously recorded for the ARIC MRI Study subjects. The ARIC visual WMH grading scale is broadly used in the field of WMH research, both in study of normal aging and in patients with acute cerebral ischemia (Liao et al, 1997; Longstreth et al, 1996; Manolio et al, 1994). MR-based WMH grade is often determined by the extent of white matter changes involving predominantly periventricular and deep subcortical regions, which are also the regions that correspond to the greatest volumetric burden of leukoaraiosis (DeCarli et al, 2005). Correlation between the median MR-based WMH grade and WMHV tertiles in this study further substantiates the utility of the AIS WMH protocol in comparison to the ARIC volumetric measure. The latter is expected to be closely associated with the ARIC WMH grades *a priori*; moreover, if both methods offered an approach to individual WMH lesion count, the association between the AIS and ARIC methods would be reinforced further.

There are limitations to using the method specifically designed to address the lack of homogeneity associated with variability in image acquisition and the artifact associated with regional intensity variations. As a result, significant operator-mediated input is required to adjust for potential variability in deriving the final WMH map; furthermore, intense training procedures are required to assure high inter-rater agreement rate between the certified operators (Rost et al, 2010a). However, these protocol specifications are the necessary minimal requirements for a WMHV quantification method, which is adapted to obtain reliable measurements from clinical MRI scans of AIS patients, as opposed to the research-specific WMHV protocols.

Accurate assessment of the MR-detected WMH burden is important for a multitude of ongoing research studies and the future models of risk and outcome prediction in subjects with stroke and other cerebrovascular disease (Kochunov et al, 2009). Accuracy is defined as closeness of agreement between a measured quantity value and a true quantity value of a measurement. In volumetric assessment of WMH for the ARIC MRI Study subjects, a true quantity value of a measurement was estimated using a validated method (Gottesman et al, 2010; Mosley et al, 2005).

In this analysis, we have compared another validated volumetric protocol designed to measure WMH in subjects undergoing clinical MRI scans for evaluation acute cerebral ischemia with the ARIC method in order to assess the agreement between the two measurements (Rost et al, 2010). Both methods have independently demonstrated high degree of precision, or reproducibility (the degree to which repeated measurements produce similar results under unchanged conditions); furthermore, this analysis demonstrated for the first time the measurement of agreement between the gold standard method of WMH assessment and the method that can be applied to a broad pool of the clinical MRI scans for the future studies of the leukoaraiosis in stroke and other manifestations of the clinically significant cerebrovascular disease. These data could also facilitate studies of WMH across different patient populations.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions.

Abbreviation key

AIS	acute ischemic stroke
ARIC	Atherosclerosis Risk in Communities study
IQR	interquartile range
TIV	total intracranial volume
WMH	white matter hyperintensity
WMHV	white matter hyperintensity volume

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Highlights

- White matter hyperintensity (WMH) burden is a potent stroke risk factor
- Use of clinical MRI scans in research is fraught with methodological limitations
- Novel volumetric method overcomes limitations to quantify WMH in stroke patients
- It correlates highly with gold standard and is specific for WMH in ischemic stroke
- Accuracy of clinical MRI assessment is important for future large-scale studies

Figure 1. Magnetic resonance imaging-based volumetric analysis of white matter hyperintensity volume using the AIS method

A representative axial T2 FLAIR sequence with WMH is converted into Analyze format (A), and a region-of-interest map is drawn over the WMH (B). The intersection between a semi-automated signal intensity thresholding maps (C) and WMH ROI is manually edited to yield the final WMH maps (D).

Figure 2. Correlation between the WMHV measurements in 120 individuals with T2 FLAIR axial MRI assessed by the AIS WMH and ARIC methods

Abbreviations: AIS WMH: acute ischemic stroke white matter hyperintensity method; ARIC: the Atherosclerosis Risk In Communities study; WMHV: WMH volume

Figure 3. Blant Altman analysis of the measurement agreement between the WMHV estimates obtained by the AIS WMH and ARIC methods

Abbreviations: AIS WMH: acute ischemic stroke white matter hyperintensity method; ARIC: the Atherosclerosis Risk In Communities study; MGH: Massachusetts General Hospital; WMHV: WMH volume

Figure 4. Close correlation between the WMH outlines obtained using the two volumetric methods

*While the total amount of WMHV per scan appeared to be underestimated when using the AIS WMH protocol, the high validity of the measurement and degree of correlation between the WMH outlines at every individual consecutive axial image is evident. **Panel A:** WMH is visualized on T2 FLAIR axial MRI as bright signals in the periventricular, subcortical hemispheric regions bilaterally. **Panel B:** WMHV is outlined using the AIS WMH volumetric protocol (total WMHV 3.2cm³; only the right hemisphere segmentation maps are shown). **Panel C:** WMHV is outlined to match the ARIC protocol estimate on the same T2 FLAIR axial scan (total WMHV 8.6cm³; only the right hemisphere segmentation maps are shown).*

Table 1

Comparison of the two volumetric methods utilized in this study

	Sequences analyzed	WMH maps software used	WMH signal intensity	Operator's input	Total WMH volume estimates	WMHV adjustment
AIS method	Axial FLAIR	<i>MRIcro</i> (Nottingham, UK)	Automated threshold, followed by manual visual adjustment	Significant (initial ROI outlines, intensity threshold adjustment, final ROI edits)	WMHV from the hemisphere contralateral to acute ischemia is doubled	Adjusted for head size calculated as ICA on T1 sagittal MR
ARIC method	Axial FLAIR	<i>FLAIR histoseq</i> (Jack et al, 2001)	Assigned based on 1 of 3 categories (brain, CSF, WMH)	Minimal (manual editing of the automatically generated WMH maps to exclude infarcts)	WMHV is the sum of periventricular and subcortical white matter signal abnormality	Adjusted for TIV standardized to a mean of 1500cm ³

Abbreviations: AIS: acute ischemic stroke; ARIC: the Atherosclerosis Risk In Communities study; FLAIR: fluid-attenuated inversion recovery; ICA: intracranial area; ROI: region of interest; TIV: total intracranial volume; WMH: white matter hyperintensity; WMHV: WMH volume

Table 2

Volumetric measurements of WMH in 120 individuals with T2 FLAIR axial MRI assessed by the AIS WMH and ARIC methods.

	All data	Tertile 1	Tertile 2	Tertile 3
AIS method				
WMHV, cm ³ median (IQR)	3.54 (2.11 – 7.19)	1.86 (1.37 – 2.43)	3.60 (2.73 – 4.70)	11.99 (6.74 – 25.18)
ARIC method				
WMHV, cm ³ median (IQR)	7.88 (5.70 – 13.55)	4.66 (3.94 – 5.73)	8.08 (7.00 – 9.81)	22.18 (13.55 – 27.74)

Abbreviations: AIS WMH: acute ischemic stroke white matter hyperintensity method; ARIC: the Atherosclerosis Risk In Communities study, IQR: interquartile range, WMHV: WMH volume

Table 3

Association between the visual WMH grading scale and volumetric assessment of WMH severity in 120 subjects with T2 FLAIR axial MRI. *Panel A*: association between the WMH grade and the WMHV estimates obtained using the two volumetric methods. *Panel B*: association between the tertile of the WMHV obtained using the ARIC and AIS WMH methods and a corresponding WMH grade.

Panel A.		
WMH grade	ARIC WMHV, cm ³ median (IQR)	AIS WMHV, cm ³ median (IQR)
0 – 1	5.43 (4.25 – 6.68)	1.92 (1.42 – 2.66)
2	7.76 (6.64 – 10.35)	3.65 (2.62 – 4.72)
3+	23.74 (12.9 – 36.55)	13.95 (7.37 – 25.36)

Panel B.			
	WMH grade (median, IQR)		WMH grade (median, IQR)
ARIC WMHV Tertile 1	1 (1 – 1)	AIS WMHV Tertile 1	1 (1 – 1)
ARIC WMHV Tertile 2	2 (1 – 2)	AIS WMHV Tertile 2	2 (1 – 2)
ARIC WMHV Tertile 3	3.5 (3 – 5)	AIS WMHV Tertile 3	3 (3 – 5)

Abbreviations: AIS WMH: acute ischemic stroke white matter hyperintensity method; ARIC: the Atherosclerosis Risk In Communities study, IQR: interquartile range, WMHV: WMH volume